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Extended Research Article

Effectiveness of Escitalopram and Nortriptyline on Depressive Symptoms in Parkinson's disease: the ADepT-PD RCT pilot

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Scientific summary

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Scientific summary

Background

The Antidepressants for depression in people with Parkinson's Disease (ADepT-PD) trial was a three-armed randomised placebo-controlled trial to test the effectiveness and cost-effectiveness of a tricyclic and a selective serotonin re-uptake inhibitor (SSRI) on depression in people with Parkinson's disease (PD) with an internal pilot study. The tricyclic nortriptyline (target dose 100 mg), and the SSRI escitalopram (target dose 20 mg) were compared to placebo, in addition to available standard psychological care.

Objectives

Primary objective

The aim of the ADepT-PD trial was to determine the clinical effectiveness and cost-effectiveness of an 8-week course of nortriptyline (target dose 100 mg), the SSRI escitalopram (target dose 20 mg) in the treatment of depression in PD. The primary outcome was the Beck Depression Inventory (BDI) II at 8 weeks of treatment.

Secondary objectives

The secondary objectives of the ADepT-PD trial were to assess efficacy on a number of secondary outcome measures including another depression measure, the Patient Health Questionnaire-9 items (PHQ-9); the Parkinson Anxiety Scale; the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS); levodopa-equivalence dose; EuroQol-5 Dimensions, five-level version (EQ-5D-5L); Shortened Client Service Receipt Inventory; ICEpop CAPability index measure; Carer EQ-5D-5L and Carers Quality of Life Questionnaire Parkinsonism; Patient-reported Global Clinical Impression scale; Montreal Cognitive Assessment (MoCA); Scales for Outcomes in Parkinson's disease-sleep; demographic data, comorbidities, medication modified; assessment of participant's awareness of allocated treatment arm; and repeat assessments at 26 and 52 weeks.

Methods

The ADepT-PD trial was funded to be a definitive, multisite, three-arm, placebo-controlled, double-blind, Phase IV randomised controlled trial in response to a commissioning brief set by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme. The trial had an internal pilot phase with prespecified go/no-go criteria.

The trial aimed to randomise participants (1 : 1 : 1) into either the nortriptyline group – 12-month course of up to 100 mg of nortriptyline per day; the escitalopram group – 12-month course of up to 20 mg of escitalopram per day; or the control group – 12-month course of matched placebo.

Results

Screening and recruitment

A total of 1396 patients were screened for entry onto the trial, but only 52 patients were recruited and randomised into the ADepT-PD trial. Seventeen participants were randomised to the escitalopram group, 16 to the nortriptyline and 19 participants were randomised to the control group.

Completion of primary end point and withdrawals

Five out of 52 (9.6%) withdrew before the primary end point, including one before administration of the investigational medicinal product. Of the participants randomised, 16 out of 17 in the escitalopram group, 14 out of 16 in the

nortriptyline group and 17 out of 19 in the placebo arm completed the 8-week assessment. Of the 52 participants randomised, 1 participant (in the escitalopram group) withdrew due to a serious adverse event.

Clinical outcomes

All allocated arms saw a reduction in their BDI-II total score from baseline to week 8, including the placebo. In the placebo arm, this was from a mean of 24.3 (standard deviation: 7.8) at baseline to 15.7 (5.8) at week 8, in the nortriptyline arm from 20.5 (3.8) to 12.6 (8.1), and in the escitalopram arm from 23.3 (8.0) to 14.6 (8.4). A generalised mixed-effects model was used to estimate the difference in BDI-II at 8 weeks post treatment between the treatment groups (separately). The model, separate for the two active treatments, included both a fixed and a random part, and included the treatment effect and baseline BDI-II measurement. When comparing each of the two active arms to the placebo, no statistically significant differences were observed with a mean change of −3.1 [95% confidence interval (CI) −8.66 to 2.53, $p = 0.28$)] for the nortriptyline versus placebo comparison, and a mean change of −0.7 (−6.11 to 4.70, $p = 0.80$) for the escitalopram versus placebo comparison. A reduction in the total score of the PHQ-9 was observed on all arms between baseline and 8 weeks. These reduced from 12.7 (3.4) to 9.6 (3.7) in the placebo arm, 9.1 (2.6) to 6.7 (3.5) in the nortriptyline arm, and 11.9 (5.2) to 7.3 (5.5) in the escitalopram arm. When these were formally compared using the same model described above, there was a statistically significant difference observed in favour of nortriptyline ($p = 0.01$) when compared to placebo (though not escitalopram vs. placebo, $p = 0.33$). No meaningful differences were observed in any other secondary outcome measures, such as the MDS-UPDRS scores (all parts), MoCA scores and adverse events.

Conclusions for practice and research

The ADepT-PD trial was terminated at the end of the pilot phase, because it did not meet its go/no-go criteria. The main issues were a low recruitment rate owing to high rate of screen failure and patient interest, difficulties in timely identifying the condition and more widespread use of the medications than expected.

Implications for future research

We would recommend that future studies in this field should concentrate on one rather than two medications, which reduces the number of ineligible patients as well as the sample size. Alternatively, a three-arm comparison with a compound not currently available but with potential added benefit may also increase recruitment rate.

Trial registration

This trial is registered as NCT03652870.

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